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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

Toshihiro SHIMIZU et al. :

Serial No. 10/017,755 : Group Art Unit 1615

Filed on October 30, 2001 : Examiner: TRAN, Susan T.

For: ORALLY DISINTEGRABLE TABLETS

DECLARATION UNDER 37 CFR 1.132

Honorable Commissioner of
Patents and Trademarks,
Washington, D.C. 20231

Sirs:

I, Toshihiro SHIMIZU, declare:

That I am a citizen of Japan residing at 15-3, Aramakiminami 2-chome, Itami-shi, Hyogo, Japan;

That I was born on July 10, 1964 in Okayama, Japan;

That I graduated from Gifu Pharmaceutical University, with degree of Bachelor of Pharmaceutical Science in March 1988;

That I have been employed by Takeda Chemical Industries, Ltd. (now, Takeda Pharmaceutical Company Limited), Osaka, Japan, since April, 1988, and have been engaged in research and development in the Pharmaceutical Production Division of said company;

That I have been appointed a Manager of Pharmaceutical Manufacturing Department of Osaka Plant in said Pharmaceutical Production Division since 2007;

That I was awarded a Ph. D in Formulation Study of Lansoprazole Fast-disintegrating Tablets containing Enteric Coated Microgranules from Kyushu University in March, 2005;

That I am a member of the Pharmaceutical Society of Japan, and have published, with other research workers, a number of reports on scientific studies, among others, including

1. Shimizu T., Nakano T., Morimoto S., Tabata T., Hamaguchi N., Igari Y., *Chem. Pharm. Bull.*, 51, 942-947 (2003)

2. Shimizu T., Kameoka N., Iki H., Tabata T., Hamaguchi N., Igari Y., *Chem. Pharm. Bull.*, 51, 1029-1035 (2003)

3. Shimizu T., Sugaya M., Nakano Y., Izutsu D., Mizukami Y., Okochi K., Tabata T., Hamaguchi N., Igari Y., *Chem. Pharm. Bull.*, 51, 1121-1127 (2003);

That I am one of the co-inventors of the above-identified U.S. Patent Application Serial No. 10/017,755 filed on October 30, 2001;

That the following Experiment was conducted by myself and under my supervision and control:

Experiment

1. Purpose

The effect of over-coating of enteric coated micro-granules with a water-soluble sugar alcohol such as mannitol on the hardness and oral disintegration time of tablets was examined.

2. Production of orally disintegrable tablets

Orally disintegrable tablets having the formulations shown in Table 1 and Table 2 were produced according to the method described below.

2.1. Production of micro-granules containing active compound

Lansoprazole, magnesium carbonate, low-substituted hydroxypropyl cellulose and hydroxypropyl cellulose were dissolved and suspended in water to give a coating suspension for an active compound layer.

Hydroxypropyl methylcellulose and talc were dissolved

and suspended in water to give a coating suspension for an intermediate layer.

Using a rotating fluidized-bed granulator (manufactured by Freund Corporation, MP-10), lactose-microcrystalline cellulose spheres were coated consecutively by spraying the coating suspension for active compound layer and the coating suspension for intermediate layer, and dried in the rotating fluidized-bed granulator.

The granules were sieved by sieves (150 μm and 300 μm) to obtain lansoprazole coated micro-granules.

2.2. Production of enteric coated micro-granules

The enteric coating components shown in Table 1 were dissolved and suspended in water to give an enteric coating suspension.

Mannitol was dissolved in water to give an over-coating solution.

Using a rotating fluidized-bed granulator (manufactured by Freund Corporation, MP-10), the lansoprazole coated micro-granules were coated consecutively by spraying the enteric coating suspension and the over-coating solution and dried in the rotating fluidized-bed granulator. The enteric coated micro-granules of Formulation 1 were not coated by spraying the over-coating solution.

The granules were sieved by sieves (180 μm and 350 μm) to obtain enteric coated micro-granules.

Table 1 Formulation of Enteric Coated Micro-granules (mg)

	Component	Formulation 1	Formulation 2
Core	Lactose-microcrystalline cellulose spheres (Nonpareil 105T)	30	30
Active compound layer	Lansoprazole	30	30
	Magnesium carbonate	10	10
	Low-substituted hydroxypropyl cellulose (LH-32)	5	5
	Hydroxypropyl cellulose	10	10
Intermediate layer	Hydroxypropyl methylcellulose 2910	4	10
	Talc	1	-
Enteric coating	Methacrylic acid copolymer LD (solid content)	83.2	73.5
	Ethyl acrylate-methyl methacrylate copolymer dispersion (solid content)	9.2	8.2
	Triethyl citrate	9.2	16.3
	Glyceryl monostearate	3.3	5.2
	Polysorbate 80	1.8	1.7
	Talc	3.2	-
	Ferric oxide	0.1	0.1
Over-coating	Mannitol	-	10
Total		200	210

2.3. Production of orally disintegrable tablets

The enteric coated micro-granules and the mixed components shown in Table 2 were blended in a polyethylene bag.

Using a rotary tableting machine (manufactured by KIKUSUI SEISAKUSHO LTD., Correct 12HUK) and a 11 mmϕ, 15R punch, tablets were produced at 30 rpm and a compression force of about 15 KN/cm^2.

Table 2 Formulation of Orally Disintegrable Tablets (mg)

	Component	OD-1	OD-2
Enteric coated micro-granules	Enteric coated micro-granules (Formulation of enteric coated micro-granules)	200 (Formulation 1)	210 (Formulation 2)
Mixed components	Mannitol	189.6	179.6
	Low-substituted hydroxypropyl cellulose (LH-33)	30	30
	Crystalline cellulose (CEOLUS KG-801)	60	60
	Crospovidone	15	15
	Anhydous citric acid	3	3
	Aspartame	0.9	0.9
	Magnesium stearate	1.5	1.5
Total		500	500

3. Evaluation of Orally Disintegrable Tablets

The obtained two kinds of orally disintegrable tablets were measured for the hardness, friability and oral disintegration time.

Hardness: Hardness of each of 10 tablets was measured using a hardness tester (manufactured by Toyama Sangyo, Co., Ltd.) and mean value was calculated.

Friability: Using a friability tester having similar functions as does the apparatus described in USP <1216> Tablet Friability (drum size was about 300 mm in the USP, but 500 mm for this test), the weight of 10 tablets was previously measured accurately, the weight of the tablets after rotation at 30 rpm for 10 minutes was measured accurately, and the friability (%) was calculated by the following formula.

Friability (%) = (weight before test- weight after test)/weight before test x 100

Oral disintegration time: The measurement of disintegration time was carried out in two healthy human subjects. After the mouth was rinsed with water, one tablet was held in the mouth until the tablet disintegrated without chewing. The disintegration time was recorded.

4. Results

The results of the measurements are shown in Table 3.

Table 3 Results of Measurements

Formulation of orally disintegrable tablets	OD-1 without over-coating	OD-2 with over-coating
Hardness (mean)	4.8 kg	6.8 kg
Friability	5.39%	0.37%
Oral disintegration time	22 sec (18-25 sec)	29 sec (27-32 sec)

5. Conclusion

From the foregoing results, it is clear that over-coating of enteric coated micro-granules with a water-soluble sugar alcohol such as mannitol affords an effect of increased hardness of the obtained orally disintegrable tablets and improved friability of the tablets, while maintaining rapid oral disintegrability.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed on this 18 day of October, 2007

Toshihiro Shimizu

Toshihiro SHIMIZU